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Trajectories in hypnotic use and approaching death: a register linked case–control study

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Abstract

Purpose: Whether the association between hypnotic and increased mortality risk is created by causation or confounding, has been long debated. We examined further the possibility of confounding by indication with a comprehensive approach.

Methods: The National FINRISK Study cohorts of 1997, 2002, and 2007 (25,436 participants aged 25–74) were followed up until July 2012. There were 1,822 deaths, and at least one gender, baseline age and cohort matched 'control' was found for 1,728 'cases' yielding a final analytical sample of 3,955 individuals. An index age, equivalent to the age at death of their respective cases' was set for each control. Hypnotic drug purchases were followed from the Finnish nationwide register during a 36-month run-up period before the date of death/index date. The prevalence and incidence of hypnotic purchases were compared between cases and matched controls. In addition, latent developmental trajectories of purchases were modelled and their relations with specific and all-cause death risks were analysed.

Results: An increasing difference between cases and controls was observed as regards the use of hypnotic drugs. During the last 30 months before the date of death/index date, the rate ratio of incident purchases between cases and controls was 2.37 (95% CL, 1.79–3.12) among older and 3.61 (95% CL, 2.37–5.89) among younger individuals. The developmental trajectories of hypnotic drug purchases were differently and by interpretation plausibly associated with specific mortality risks.

Conclusions: In most cases the association between hypnotics and mortality risk is created by symptomatic treatment when death is approaching.

Keywords: hypnotics, benzodiazepines, z-hypnotics, mortality, death causes

1. Introduction

Several studies have suggested that during the last decades insomnia-related symptoms have increased among the general population in, for instance, the UK [1], the US [2], Norway [3] and Finland [4]. The number of prescriptions for sleep medication has also increased in parallel [2, 3]. In the US, the overall increase in benzodiazepine (BZD) prescribing trends has taken place although non-benzodiazepine receptor agonists seem to have partially replaced BZDs in the treatment of sleep disorders between 1993 and 2010 [5]. In line with this, a decrease in the consumption of traditional hypnotics has been observed in Finland, but it is, however, mostly explained by a shift to small sub-clinical doses of antidepressants and some other new drugs [6]. The epidemiological data on the still continuing and perhaps even strengthening trend of insomnia treatment by pharmacological agents emphasises the importance of safety issues regarding long-term use of sleep medication.

Already in 1979, the authors of the re-analyses of the first American Cancer Prevention Study concluded that both deviant from population mean sleep duration and use of hypnotic medication were independently associated with future death [7]. The relative predictive risk was higher among younger than older participants, although absolute risk was naturally higher among older age groups. Since then a lively debate on the mortality risk associated with hypnotic use has taken place. Most studies suggest that hypnotic use has an association with increased all-cause and certain specific (eg cancer) mortality risks independent from several pertinent adjustments. See for example [8-11]. However, some researchers have come to more critical conclusions, see for instance [12-14]. A recent review [15] including 37 studies strongly suggests that the use of sleep medication (mainly benzodiazepines and their agonists) is associated with an increased risk of mortality. Consequently, the discussion has turned more towards the nature of the hypnotics–mortality association, that is, whether the association is causal or confounding, rather than the possible existence of the association. Notably, however, a recent study reported decreased mortality associated with the use of zolpidem [16].

Several difficult methodological problems have precluded the debate from resolving the issue. It is clear that users and non-users of hypnotic drugs differ from each other by several confounding factors influencing mortality and morbidity. First, different sleep disturbances may have synergistic risk effects with other medical conditions. Additionally, hypnotic drugs may worsen some consequences of certain sleep disturbances, such as sleep apnoea, and thereby increase mortality risk. Mental health conditions, especially depression, are associated with insomnia in a reciprocal way. Alcohol use may have serious interactions with hypnotics. These are mere examples of confounders, which are often difficult or even impossible to control for in statistical models predicting the mortality risk associated with hypnotic drug use. However, it has been concluded that the association is greatly reduced after adjusting for baseline risk factors like general health, smoking and physical functioning [12, 17]. The authors of one study emphasised that “high-risk patients take more hypnotics,

and it is this higher risk rather than the hypnotics that contributes to adverse health outcomes" [12].

In line with this, a recent a Norwegian study [18] examined a previously unstudied confounding factor and provided an alternative explanation for the hypnotics–mortality association. When the Norwegian population aged 41–80 was observed in 2010, those who died during the first 10 months of that year had a 2.3-fold risk to use hypnotic or opioid drugs when compared to those who were alive at the end of the year. Of note, as death came closer, the death cohort received drugs with an increasing proportion of users, culminating in the greatest frequency in the last few months before death [18]. Consequently, the authors concluded that "the association between hypnotic availability and mortality can be at least partially, and possibly completely, explained by an increase in symptomatic treatment of increasing discomfort as death draws near." We examined that possibility more in-depth by analysing the prevalence and incidence of hypnotic purchases from several years before death among the death and control cohorts. Furthermore, we evaluated trajectories of hypnotic drug use over the three last years before death using latent class growth curve analysis. We expected to find different hypnotic use trajectories to be differently associated with specific causes of death, which would indicate that different underlying courses of illnesses and their symptoms create different trajectories. This would explain a general association between the use of hypnotic drugs and mortality risk.

2. Methods

2.1 Selection of the study population

The study population was selected from three independent cross-sectional population surveys of the National FINRISK Study (1997, 2002, and 2007). FINRISK is a series of large cross-sectional health surveys [19]. It includes an extensive health and lifestyle questionnaire and a physical examination. Each FINRISK survey is conducted on a random sample drawn from the population register of the study regions according to standardised sampling methods [20]. Each FINRISK study has the approval of the relevant ethical committee and informed consent from all participants.

The FINRISK samples of 1997, 2002 and 2007 consisted of 25,436 participants (12,151 men and 13,285 women) aged 25–74 and living in five geographic areas in Finland. The final analytical sample was comprised in the following way. 1) *Selection of cases*. The three FINRISK samples were followed up until 22 June 2012. According to information from the National Register of Causes-of-Death, 1,822 individuals had died by that day. They are hereafter referred to as "cases" or "death cohort". 2) *Selection of controls*. An attempt was made to match each case with two personal controls. The matching criteria were gender, age (precision ± 2 years) at baseline health examination (ie, age when participating in the FINRISK survey) and the FINRISK survey itself (ie, both cases and their controls participated in the same FINRISK survey).

During the on average 7.6-year follow-up, 1,822 deaths were observed. At least one matched control was found for 1,728 (94.8%) individuals. In the 1997 FINRISK survey, among the oldest death cases (died at age 65–88) there were 415 individuals who only had one living control left. However, for cases who had died during working age (at age 26–64 years) two matched controls were always found. We analysed older cases with one matched control and younger cases with two matched controls. Consequently, at baseline (time of the FINRISK health examination) the final analytical sample consisted of 1,497 younger individuals (499 future younger death cases and their 998 personal controls) and 2,458 older individuals (1,229 future older death cases and their 1,229 personal controls). Consequently, the final analytical sample consisted of 3,955 individuals.

2.2 Analysis period

As the first step, personal index ages equivalent to the age at death of respective cases was set for all controls. For the older group, the median of this age was 74.9 in the 1997 sample, 73.1 in the 2002 sample and 72.0 in the 2007 sample. For the younger group the ages were 57.7, 57.2 and 56.6 years respectively. Then, as a second step, a 36-month time period (hereafter referred to as a run-up period) before the date of death/index date was defined for each individual. Consequently, in the beginning and the end of the run-up period all cases were exactly at the same age as their personal controls. The run-up period was then divided into 12 three-month time-windows and the participants' purchases of hypnotic drugs were analysed during the three-year run-up period. The width of the time-windows was set at three months because Finnish outpatient care only allows drug purchases for no more than three months of treatment at one time.

2.3 Exposure variable: hypnotic (N05C) drug purchases

The use of hypnotic drugs was assessed by the participants' reimbursed purchases of hypnotic prescription drugs (ATC code N05C) based on the drug purchase register maintained by the Finnish Social Insurance Institution Kela, which includes purchases of all reimbursed prescription drugs in Finland. Data were obtained from 1 January 1994 to 30 June 2012. The data include the purchase date, drug substance, amount delivered in defined daily doses (DDDs) and a person identification number for each purchase. Purchased drugs are coded according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) -classification system [21].

2.4 Background variables

Register based data were also obtained on purchases of antidepressants (N06A), anxiolytics (N05B) and antipsychotics (N05A) during the year of the FINRISK health examination. These data were used as background variables.

The FINRISK surveys provided the following background variables based on either questionnaires or health examinations: 1) Socioeconomic characteristics: civil status;

education level; household income before taxes. 2) Somatic health status and health risks: diagnosed or treated myocardial infarction, hypertension, cancer or diabetes; self-reported health; smoking; alcohol use. 3) Mental health status: depression for at least two weeks; insomnia-related symptoms; self-reported use of hypnotics, antidepressants and anxiolytics.

2.5 Outcomes

In addition to data on the date of death from the national Population Register System (until June 2012), specific causes of death were obtained until 31 December 2010 by collating the personal identity codes with the death certificate files of Statistics Finland. This yielded a definition of a specific cause of death for 1,782 deaths (82% of all deaths). The determination of the cause of death was based on medical or forensic evidence, which provide the grounds for issuing the death certificate. The causes of death were coded at Statistics Finland according to the codes of the International Classification of Diseases (ICD-10).

3. Statistical methods

For identification of matched personal controls, a SAS macro Gmatch using the Greedy algorithm was applied. Differences between cases and controls across the descriptive baseline characteristics were tested by a chi-square test in the case of categorical variables and by Anova (SAS proc glm) in the case of continuous variables. The number of new incident purchases during the whole 30-month run-up period preceding the date of death/index date were modelled using a conditional Poisson regression (SAS proc Genmod). The probability of a new incident purchase was modelled separately for each three-month time window using logistic regression (SAS proc Genmod). All programming was carried out with SAS Release 9.4.

A variable oriented approach (the above-mentioned conventional analysis of cumulative prevalence and incidence) does not take into account that neither cases nor controls are homogenous groups in their drug purchase behaviour. Threfore, we also evaluated trajectories of hypnotic purchases (yes/no within each consecutive three-month time window) over the last 30-month run-up period using the latent class growth curve analysis (LCGM) [22]. The LCGM is a semiparametric analysis, which differentiates groups of individuals based on their probability of following a similar trajectory on their drug purchasing behaviour. We used the SAS procedure Proc Traj [23, 24] where the heterogeneity of individual differences in change of outcome is summarised by a set of polynomial functions corresponding each to a discrete trajectory. A set of model parameters (i.e., intercept and slope) is estimated for each trajectory, so that magnitude and direction of change can vary freely across trajectories. In a resulting model, the slope and the intercept are fixed across individuals within a given trajectory. In other words, individual differences are modelled by the multiple trajectories included in the model. Detailed rules of model selection, underlying statistical theory, used software and its functional capabilities are available elsewhere [23, 24]. Our aim was to identify possible clusters of individuals following similar drug purchase behaviour (developmental drug purchase

trajectories) and possible differences between cases and controls. The dependent variable used was a dichotomised variable indicating within each three-month time-window whether an individual had at least one purchase of hypnotic drugs. Consequently, a series of 12 time points during a three-year run-up period was modelled.

4. Results

4.1 Descriptive characteristics of selected participants

Descriptive baseline characteristics and a comparison of the selected participants (cases and controls) stratified into two age groups are shown in Table 1. Cases and controls differed from each other as expected. Among other things, self-reported baseline use of hypnotics and the number of insomnia-related symptoms were higher and self-reported health was worse in cases than controls.

	Younger group (age at death/index age: 26–64)			**Older group (age at death/index age: 65–88)**		
	Cases n=499	**Controls n=998**	***P***	**Cases n=1229**	**Controls n=1229**	***P***
Age (years) at death (cases) and accordingly set index age (controls), mean ± SD	55.8 ± 7.7	55.8 ± 7.7	1.000	74.6 ± 5.4	74.6 ± 5.4	1.000
Matched characteristics						
Men, n (%)	345 (69.1)	690 (69.1)	1.000	821 (66.8)	821 (66.8)	1.000
Women, n (%)	154 (30.9)	308 (30.9)		408 (33.2)	408 (33.2)	
Age (years) at baseline, mean ± SD	49.7 ± 8.5	49.7 ± 8.5	0.997	66.4 ± 5.1	66.3 ± 5.1	0.692
Socioeconomic characteristics						
Civil status Lives alone, n (%)	203 (40.7)	242 (24.3)	<.0001	431 (35.1)	338 (27.5)	<.0001
Education level Basic, n (%)	233 (47.2)	386 (38.7)	0.006	834 (68.9)	755 (62.0)	0.0005
Education level Secondary, n (%)	212 (42.9)	485 (48.6)		301 (24.9)	351 (28.8)	
Education level Higher, n (%)	49 (9.9)	127 (12.7)		75 (6.2)	112 (9.2)	
Household income before taxes						
Low ≤ 16, 820 euros/year, n (%)	162 (33.5)	161 (16.5)	<.0001	530 (46.3)	415 (34.8)	<.0001
Intermediate 16,821 – 42,051 euros/year, n (%)	219 (45.3)	459 (47.0)		483 (42.2)	562 (47.2)	
High ≥ 42,051 euros/year, n (%)	103 (21.3)	357 (36.5)		133 (11.6)	215 (18.0)	
Somatic health status and health risks at baseline						

Diagnosed myocardial infarction Yes, n (%)	29 (5.9)	15 (1.5)	<.0001	166 (15.2)	101 (8.5)	<.0001
Diagnosed or treated hypertension Yes, n (%)	154 (31.1)	284 (28.7)	0.334	541 (45.1)	477 (39.1)	0.003
Diagnosed or treated cancer Yes, n (%)	26 (5.4)	8 (0.8)	<.0001	63 (5.8)	47 (4.0)	0.047
Diagnosed or treated diabetes Yes, n (%)	51 (10.5)	46 (4.7)	<.0001	176 (16.3)	107 (9.2)	<.0001
Self-reported health Fairly or very bad, n (%)	114 (23.1)	99 (10.0)	<.0001	254 (23.1)	122 (10.3)	<.0001
Body mass index, mean ± SD	27.6 ± 5.4	27.5 ± 4.5	0.564	28.3 ± 4.9	27.9 ±4.0	0.042
Smoking Smoke currently n (%)	251 (50.5)	267 (26.9)	<.0001	303 (27.7)	118 (10.0)	<.0001
Alcohol Intoxicated no more than twice per month n (%)	216 (44.6)	503 (51.8)	0.0005	401 (37.1)	425 (37.0)	0.115
Alcohol Intoxicated more often n (%)	158 (32.6)	224 (23.1)		115 (10.7)	94 (8.2)	
Mental health status, sleep, use of psycholeptic (N05) and antidepressant (N06A) drugs at baseline						
Depression for at least two weeks Yes, n (%)	160 (32.4)	205 (20.7)	<.0001	245 (20.9)	187 (15.5)	0.0007
Self-reported use of antidepressants During last month or earlier n (%)	83 (17.3)	103 (10.5)	0.0002	142 (13.4)	111 (9.5)	0.004
Register based purchases of antidepressants (N06A) At least one purchase during the baseline year	66 (13.2)	69 (6.9)	<.0001	127 (10.3)	83 (6.8)	0.002
Insomnia-related symptoms During last month: occasionally or often	263 (54.0)	456 (46.4)	0.006	606 (52.8)	591 (49.2)	0.083
Self-reported use of hypnotics During last month n (%)	72 (14.9)	66 (6.7)	<.0001	193 (18.1)	157 (13.4)	0.004
Self-reported use of hypnotics 1-12 months ago or earlier n (%)	101 (21.0)	119 (12.1)		166 (15.6)	166 (14.2)	
Register based purchases of hypnotics (N05C) At least one purchase during the baseline year n (%)	74 (14.8)	61 (6.1)	<.0001	232 (18.9)	139 (11.3)	<.0001
Self-reported use of anxiolytics During last month n (%)	60 (12.4)	44 (4.5)	<.0001	98 (9.3)	79 (6.8)	0.080
Self-reported use of anxiolytics 1-12 months ago or earlier n (%)	67 (13.8)	85 (8.7)		125 (11.8)	131 (11.2)	
Register based purchases of anxiolytics (N05B) At least one purchase during the baseline year n (%)	75 (15.0)	43 (4.3)	<.0001	138 (11.2)	114 (9.3)	0.111
Register based purchases of antipsychotics (N05A) At least one purchase during the baseline year n (%)	38 (7.6)	18 (1.8)	<.0001	91 (7.4)	32 (2.6)	<.0001

Table 1. Descriptive characteristics of selected participants included in the study by age groups at baseline in the National Finrisk Study cohorts of 1997, 2002, and 2007

4.2 Purchases of hypnotic (N05C) drugs

4.2.1 Initial prevalence

The prevalence of hypnotic (N05C) purchases differed significantly between cases and controls during the three-year run-up time before the date of death/index date. The run-up period was divided into 12 time-windows, three-months each. We considered that the first two time-windows (months 36–31 before the date of death/index date) would reveal current hypnotic users at that time. The initial six months prevalence figures were 3.7% among younger controls, and 8.0% among older controls. The corresponding figures were 11.4%, and 16.2% among cases, respectively. (See also Table 2).

4.2.2 Cumulative incidence after the initial 6 months phase of the run-up period

After the initial six-month period (months 30–1 before the end of the run-up period), cumulative incidence was calculated for each three-month time-window and a rate ratio in each time-window was calculated between cases and controls in both age groups. The resulting 30-month cumulative incidence of new buyers was 4.3% among younger controls, and 6.9% among older controls. The corresponding figures were 14.4%, and 14.8% among cases, respectively. (See also Table 2.) A graphical illustration for the older age group is shown in Figure 1. Across the whole 30-month period, the rate ratio estimate of incident purchases between cases and controls among the older study group was 2.37 (95%CL 1.79–3.12), and among the younger study group 3.61 (95%CL 2.37–5.89). The number of new incident users was analysed with pertinent explanatory variables using multivariable conditional Poisson regression with robust error variance (Table 2).

[Figure 1 about here; single column; in colour]

Figure 1. Cumulative incidence of new buyers of hypnotic drugs among the older age group during the last 30-months preceding the date of death/index date

Especially during the last three months before the date of death/index date, the increase in rate ratio among the older age group was remarkable (Figure 2), which indicates that the incidence rate of new buyers was several times higher among cases than controls. However, among the younger subgroup, only few incident cases were revealed within each separate three-month time-window and, consequently, confidence intervals for separate estimates were too large to infer anything about the possible time trend of rate ratio estimates in the younger study group.

[Figure 2 about here; single column, balck and white]

Figure 2. Rate ratio estimates of new incident buyers for each time-window during the last 30 months between cases and controls among the older study group

The results of multivariable conditional Poisson regression models are shown in Table 2.

Models	Initial 6 months prevalence of N05C purchases				30 months cumulative incidence of new buyers			
	Younger study group (age at death/index age 26–64)		Older study group (age at death/index age 65–88)		Younger study group (age at death/index age 26–64)		Older study group (age at death/index age 65–88)	
	RR	**95% CL**	**RR**	**95% CL**	**RR**	**95% CL**	**RR**	**95% CL**
Model I (initial model with condition case/control and gender)								
Case (ref control)	**3.10**	2.09 - 4.60	**1.92**	1.54 – 2.40	**3.39**	2.28 – 5.03	**2.37**	1.79 – 3.12
Women (ref men)	**1.53**	1.04 – 2.25	**1.56**	1.27 – 1.91	1.37	0.92 – 2.04	1.21	0.92 – 1.58
Model II = Model I + Sociodemographic factors*								
Case (ref control)	**2.96**	1.98 – 4.42	**1.90**	1.52 – 2.39	**3.44**	2.30 – 5.16	**2.34**	1.79 – 3.06
Women (ref men)	**1.49**	1.01 - 2.20	**1.52**	1.22 – 1.89	1.37	0.93 – 2.01	1.20	0.93 – 1.57
Model III = Model I + Somatic health factors at baseline**								
Case (ref control)	**2.41**	1.47 – 3.98	**1.50**	1.16 – 1.95	**2.98**	1.95 – 4.56	**2.33**	1.72 – 3.15
Women (ref men)	**1.82**	1.17 - 2.84	**1.76**	1.32 – 2.35	1.40	0.91 – 2.17	**1.62**	1.20 – 2.21
Self/reported health bad (ref very or fairly good)	**2.18**	1.37 – 3.46	**1.70**	1.30 – 2.21	1.05	0.50 – 1.56	1.36	0.98 – 1.89
Cancer yes (ref no)	0.28	0.04 – 2.15	**1.51**	1.00 – 2.27	**2.04**	1.00 – 4.17	1.46	0.91 – 2.33
Hypertension yes (ref no)	1.37	0.88 – 2.12	1.24	0.98 – 1.58	1.27	0.85 – 1.88	**1.41**	1.07 – 1.84
Alcohol: drunken at least 2 times/month (ref not once)	1.08	0.66 – 1.79	1.34	0.85 – 2.09	1.29	0.82 – 2.00	**1.84**	1.29 – 2.62
Model IV = Model I + Mental health factors at baseline***								
Case (ref control)	**2.20**	1.51 – 3.20	**1.76**	1.43 – 2.17	**2.91**	1.96 – 4.32	**2.30**	1.76 – 3.00
Women (ref men)	1.19	0.82 – 1.73	**1.31**	1.08 - 1.60	1.29	0.89 – 1.87	1.14	0.89 – 1.47
Insomnia symptoms yes (ref no)	**4.72**	3.26 – 6.83	**4.30**	3.47 – 5.34	**2.63**	1.69 – 4.08	**1.99**	1.44 – 2.74
Purchases of antidepressants (N06A) during baseline year yes (ref no)	**1.92**	1.25 – 2.95	**1,67**	1.29 – 2.18	**1.81**	1.05 – 3.14	1.29	0.83 – 2.00
Purchases of anxiolytics (N05B) during baseline year yes (ref no)	**2.51**	1.63 – 3.87	**1.61**	1.25 – 2.07	1.50	0.88 – 2.54	1.44	0.97 – 2.15

*Sociodemographic factors: Not shown non-significant effects of civil status, education level and household income before taxes

** Somatic health factors at baseline: Not shown non-significant effects of diagnosed myocardial infarction, diabetes, body mass index and smoking

*** Mental health factors at baseline: Not shown non-significant effect of purchases of antipsychotics

Table 2. Multivariable conditional Poisson regression models providing RR estimates predicting the initial six months (the 36–31 months before the date of death/index date) prevalence of hypnotic purchases and the later 30 months (the following 30–1 months) cumulative incidence of new buyers. Statistically significant estimates are shown in bold.

The results of the multivariable conditional Poisson regression models revealed that the RR estimates between cases and controls were not substantially attenuated when pertinent sociodemographic (Table 2, Model II), somatic (Table 2, Model III) or mental (Table 2, Model IV) baseline health factors were accounted for.

4.2.3 Developmental trajectories of N05C purchases

At first, models with 2, 3, 4 and 5 trajectory groups were fit into the whole analytical study sample. The models were compared by the Bayesian information criterion (BIC) and the log Bayes factor was calculated when the different numbers of trajectories in nested models were tested. These comparisons revealed very strong evidence (the log Bayes factor between the models with 4 and 5 trajectories was 143.2) that the model with 5 trajectories fitted the data best. The reliability (the average posterior probability of group membership) of its trajectories was very good (0.806–0.987). The interpretation of the trajectory groups was plausible and although four groups had less than five percent prevalence, it was chosen as the best model for the data (Figure 3).

[Figure 3 about here; single column; colour]

Figure 3. The developmental latent trajectories of N05C purchases during the three-year run-up period before the date of death/index date. (12 three-month time-windows).

The first trajectory was named “continuously increasing use”. Its prevalence was 3.4%. Persons in this group were characterised by a steady linear increase in their hypnotic use throughout the whole three-year period. The second trajectory, “non-users”, had a prevalence of 84.5%. Characteristic of this group was a continuous lack of hypnotic purchases. The third group was named “continuously decreasing use” and had a prevalence of 4.7%. This group was characterised by a steady linear decrease in N05C purchases during the whole three-year period. The fourth group, ”new users during the end period”,

consisted of persons who had very few purchases during the first year but rapidly increasing purchases during the last two years. The prevalence of this group was 2.8%. The fifth group was named “continuously high use”. Its prevalence was 4.6% and its members were characterised by a relatively steady and frequent use of hypnotics. According to the maximum-probability assignment rule, each individual was then grouped between the trajectories. After that, the distribution of cases and controls between trajectories was tested. As expected, the distribution differed statistically significantly (Chi-Square 140.8 (3955) df=4, p<.0001) (Table 3).

Trajectory group	Cases	Controls	All n
1 “Continuously increasing use”	72 (59.5%)	49 (40.5%)	121
2 “Non-users”	1348 (39.9%)	2032 (60.1%)	3,380
3 “New users during the end period”	119 (69.2%)	53 (30.8%)	172
4 “Continuously decreasing use”	67 (70.5%)	28 (29.5%)	95
5 “Continuously high use”	122 (65.2%)	65 (34.8%)	187
All	1,728 (43.7%)	2,227 (56.3%)	3,955

Table 3. Distribution of cases and controls across five drug use trajectory groups

The prevalence of cases (in other words the death risk) was approximately 2.1–3.5-fold in different user trajectory groups when compared with non-users. To test whether user groups differed from each other as regards the case–control distribution, gender and age adjusted relative risk (RR) estimates of being a case vs a control were calculated using the “non-users” group as reference. The relative risk of all-cause mortality was found to not differ statistically significantly between trajectory groups 1, 3, 4 and 5. See Table 4.

Trajectory group	RR	95% Confidence limits
2 “Non-users”	ref	
1 “Continuously increasing use”	2.1	1.45 – 3.05
3 “New users during the end period”	3.49	2.23 – 5.46
4 “Continuously decreasing use”	3.36	2.41 – 4.70
5 “Continuously high use”	2.66	1.95 – 3.62

Table 4. Relative risk (RR) estimates of deaths adjusted for gender and age by trajectory groups using “non-users” as reference

However, different developmental hypnotic drug use trajectories reflected different underlying medical conditions. The distribution of baseline medical conditions across trajectory groups is shown in Table 5.

Baseline medical condition	Trajectory 2 Non-users	Trajectory 1 Continuously increasing use	Trajectory 3 New users during the end period	Trajectory 4 Continuously decreasing use	Trajectory 5 Continuously high use	Chi-square P
Myocardial infarction	8.3%	7.7%	14.8%	9.2%	14.1%	0.007
Hypertension	35.5%	29.0%	40.0%	35.2%	45.1%	<.0001
Cancer	3.5%	9.4%	5.6%	5.5%	4.7%	0.017
Depression	4.2%	14.7%	7.1%	11.9%	14.3%	<.0001

Table 5. Distribution of baseline illnesses within 5 drug use trajectory groups

The baseline conditions of cardiovascular diseases (myocardial infarction and hypertension) were associated with future hypnotic use trajectories 3 (new users during the end period) and 5 (continuously high use). Highest cancer prevalence was found among trajectory 1 (continuously increasing use) and highest prevalence of depressive symptoms among trajectories 1 (continuously increasing use), 5 (continuously high use), and 4 (continuously decreasing use).

In addition, and more importantly, specific causes of death characterised different developmental hypnotic drug use trajectories. Table 6 shows statistically significant RR estimates of specific causes of death (1,417 cases) using the non-users group as a reference group.

Death cause: ICD-10 codes	Trajectory 1 Continuously increasing use	Trajectory 3 New users during the end period	Trajectory 4 Continuously decreasing use	Trajectory 5 Continuously high use
Malignant neoplasms (cancer): C00–C97	1.6 (0.028)	3.5 (<.0001)		
Degenerative diseases of the nervous system (dementia, Alzheimer): F00–F09; G30			3.4 (0.002)	
Hypertensive diseases: I10–I15	4.5 (0.050)			
Ischaemic heart diseases: I20–I28				1.8 (0.002)
Pneumonia: J00–J99	3.0 (0.012)			2.6 (0.013)
Diseases of the liver: K70–K77			5.3 (0.003)	
External causes of accidental injury, excluding transport accidents: W00–X59; Y00–Y34			2.2 (0.034)	
Intentional self-harm (suicide): X60–X84		7.6 (<0.001)		

Table 6. Relative risk (RR) estimates of specific causes of death in different developmental hypnotic drug use trajectories (non-users as reference) adjusted for gender and age.

When compared with the trajectory group 2 (non-users), continuously high use of hypnotics (trajectory group 5) was associated with increased risk of death caused by ischemic heart diseases and pneumonia. Continuously increasing use of hypnotics (trajectory 1) was associated with increased risk of death caused by cancer (mostly breast cancer), hypertensive disease, and pneumonia. Trajectory group 3, characterised by a rapidly increasing number of new individuals making purchases during the end period, was associated with increased risk of death caused by cancer and suicide. Continuously decreasing purchases of hypnotics (trajectory 4) were associated with increased risk of death caused by degenerative diseases of the nervous system, diseases of the liver and external accidental injury excluding transport accidents. See Table 6.

5. Discussion

Our main results indicate that the use of hypnotic drugs was associated with future death in several ways. 1) In the baseline health examination (5–15 years before the end of the follow-up), the proportion of hypnotic users was significantly higher among members of the death cohort, or cases, than among controls. The death cohort also had more insomnia-related symptoms and worse self-reported health. 2) This difference between cases and controls increased when death approached, and resulted in a two to three times higher prevalence of hypnotic users during months 36–31 before the date of death/index date among members of the death cohort than among controls. 3) During the last 30-month run-up period, the cumulative incidence of new users was also two to three times higher among cases than controls. 4) The difference in incidence rate of new users increased steeply between older cases and controls during the last three months. 5) During the 36-month run-up period before the date of death/index date, we found five different developmental drug purchase trajectories, four of which were associated with increased risk of death when compared with the non-users reference trajectory. 6) Different specific causes of death characterised different developmental hypnotic drug use trajectories.

5.1 The role of follow-up time length and age

The length of the follow-up time in previous studies has varied greatly in association with mortality risk estimates. The association of hypnotic drug use with mortality has been generally stronger in studies with shorter follow-up time lengths than in longer studies [15]. In previous follow-up studies, one of the shortest time lapses between any hypnotic drug exposure (mean eight pills/year) and prospective death risk was an average of 2.5 years' follow-up [8] giving also one of the highest risk estimates (3.6 times higher hazard of dying). Based on previous studies, it has been inferred that the greatest hazard is associated with initial drug doses [25]. However, at the same time deaths during the first year after baseline are often excluded, resulting in an emphasis of "the hypnotic survivors rather than the high initial risk" [25].

In our study, we found that both self-reported and reimbursement-based register data indicated higher prevalence of hypnotic users among the death cohort than among their age, gender and health examination date matched controls already in the beginning of an average of 7.6-year follow-up period. Among younger participants, the self-reported difference was 2.2-fold and the register-based difference 2.4-fold, among older participants the differences were 1.3-fold and 1.7-fold, respectively. This is similar to how the hypnotic–mortality risk association has usually shown in previous studies. It has been suggested that the association arises early in the period of drug use and continues to exist even after hypnotics are discontinued [9]. We found that the difference in the initial baseline prevalence of hypnotic users between cases and controls increased further during the follow-up period and was two to three-fold during the first six months in the beginning of the three-year run-up period before the date of death/index date. Overall, during the 2.5-year run-up period before the date of death/index date, the cumulative incidence of new purchases among cases was also two to three times that of controls. Among older participants, that difference in cumulative incidence increased extremely steeply during the final three months before the date of death/index date. That was preceded by a sharp dip in the difference between cases and controls six to four months before the date of death/index date. Our interpretation of this dip is that this point, among cases, approaching death causes several institutionalisations or hospitalisations. Therefore, the future use of hypnotics among these individuals was no longer reflected in the drug purchase register, which only covers outpatient care. Because there were only few new incident cases among younger individuals within each three-month time-window, we were unable to statistically confirm the dynamics of cumulative incidence in younger participants. Therefore, it is difficult to conclude whether our results on cumulative incidence of hypnotic purchases corroborate the suggestion that the hypnotic–mortality association is more easily seen among younger than older adults [17]. However, the difference between cases and controls in overall 30-month cumulative incidence was somewhat greater among younger than older individuals. These results are in line with analogous recent findings, where during a 24-month run-up period before the date of death/index date the prevalence of hypnotic users increased as death neared in the death cohort but not among the control group, and the greatest difference was found in the younger age group [18].

The previously reported influence of follow-up time length on mortality estimates probably reflects differences in the development of individual drug use histories or trajectories among cases and controls in time. It is clear that hypnotic users are not a homogeneous group. As regards their hypnotic use behaviour in time, they form a mixture of different subgroups. It has been stressed [15] that in studies with long follow-up periods predicting mortality risk with baseline drug use, participants who used hypnotics at baseline may not necessarily continue their use over the whole follow-up period. In addition, control participants may start to use hypnotics after the baseline assessment. Consequently, “the actual hypnotic consumption of the control group would more and more approximate that of the baseline hypnotic users” [15]. The person-oriented analysis, modelling individual developmental hypnotic use trajectories, can therefore importantly increase our understanding of the underlying mechanisms behind the hypnotic–mortality association.

5.2 Developmental drug use trajectories and specific mortality causes

To our best knowledge, all previous studies have used a conventional variable oriented approach in their analyses. We analysed a three-year run-up period before the date of death/index date among all participants using a person-oriented approach the latent class growth curve analysis and found five different developmental drug purchase trajectories, four of which were associated with increased risk of death when compared with the non-users', reference trajectory. Taken together, relative risk estimates were statistically of the same size between risk groups and varied between 2.10 and 3.49.

Upon discussing "the use of hypnotics and prospective mortality risk", an important question has been whether hypnotics are associated with specific causes of death. Several previous studies have lacked data on the causes of death. Studies including this information have suggested that the use of hypnotics may be associated with some specific causes of death, such as suicide [26, 27], coronary artery disease [26], dementia and Alzheimer's disease [28], and cancer [8, 11]. In our study, an important and new finding was that different developmental trajectories of hypnotic drug use were differently associated with specific (including the above-mentioned) causes of death. When compared with "non-users", the trajectory "continuously increasing purchases" was associated with increased risk of death by cancer (mainly by breast cancer), hypertensive diseases and pneumonia. The trajectory "new purchases during the end period" was associated with increased risk of death caused by cancer and suicides. The trajectory "continuously decreasing purchases" was associated with increased risk of death caused by degenerative diseases of the nervous system (dementia, Alzheimer's disease), diseases of the liver and external causes of accidental injury except transport accidents. Finally, the trajectory "continuously high use" was associated with increased risk of death caused by ischaemic heart diseases and pneumonia. In general, these results clearly support the assumption of reverse causation or confounding by indication, as has been recently suggested [18].

The wide range of different causes of death, associated with the use of hypnotics, suggest that there is no specific single mechanism behind the hypnotic–mortality risk association. There are most probably several underlying mechanisms creating the association. It has been emphasised that most patients who are prescribed hypnotics are multimorbid [29]. Purchase register data does not reveal why hypnotics are bought. However, it is plausible that sleeping problems and discomfort related to specific diseases like degenerative diseases of the nervous system and/or multimorbidity are often behind the prescription of hypnotics, although a clear-cut indication may be lacking [29]. Indirectly, the assumption is also supported by the recent finding that in most cases when physicians prescribe hypnotics they record no indication of insomnia or another medical reason for the prescription [15]. Against this background, our trajectories are interpreted as follows. Either those with "continuously increasing purchases" are increasing the frequency of their drug purchases or the group is gaining new incident users. It is plausible that this kind of behaviour is associated with increased symptomatic treatment of discomforts caused by approaching death by (breast) cancer, hypertensive diseases and pneumonia.

Among the group of “new purchases during the end period” new incident cases of hypnotic users accumulate rapidly during the last 1.5 years before the date of death/index date although there were very few purchases before that. This kind of behaviour is plausibly explained by symptomatic treatment of rapidly worsening (mental) health problems leading to suicide as well as symptomatic treatment of discomfort caused by rapidly progressive cancer.

Within the frame of continuous purchases, there is a linear trend of discontinuation of drug purchases when the date of death/index date is approaching among members of the trajectory group “continuously decreasing purchases”. A plausible explanation is that degenerative diseases of the nervous system (dementia, Alzheimer’s disease), diseases of the liver and external causes accidental injuries caused the hospitalisation or institutionalisation of these patients and therefore their drug use is no longer reflected in the reimbursement register, which only covers outpatient treatment. However, deaths caused by external causes of accidental injury, excluding transport accidents, may also be related to hangover effects, such as daytime sedation, reduced vigilance and psychomotor impairment caused by the hypnotics themselves [30-32]. The discontinuation of drug purchases could theoretically also be interpreted as a sign of remission. This is, however, not believable because the trajectory was associated with increased mortality risk. Finally, the high frequency of hypnotic purchases among the members of the trajectory group “continuously high use” is plausibly explained by symptomatic treatment of discomfort caused by ischaemic heart diseases. Altogether we feel that the finding of specific causes of death associated with different specific drug use trajectories in time strongly supports the interpretation of the hypnotics-mortality association being, at least in most cases, caused by confounding by indication as Neutel and Johansen have suggested [18].

5.3 Strengths and limitations of the study

Our study has several strengths when compared with many earlier studies. First, we used register databases to identify hypnotic drug purchases without any loss in follow-up and specific causes of death. According to the annual wholesale statistical database compiled by the Finnish Medicines Agency FIMEA, from 1 January 2006 to 31 December 2010 the purchase register of the Finnish Social Insurance Institution Kela included data on 81% of the total outpatient consumption of hypnotic (N05C) drugs giving a relatively strong confidence on our estimate of hypnotic drug use [6]. Based on a health examination and questionnaires in the beginning of the follow-up we had information on background characteristics regarding the individuals’ health status, drug use, life style factors and socioeconomic status. We were able to define the exposure to hypnotic drugs. Furthermore, our prevalence models were adjusted for register-based use of antidepressants, anxiolytics and antipsychotics confirming that they did not explain the difference in hypnotics between cases and controls. An important strength is that, according to our best knowledge, our study adds a new, person-oriented analysis to previous studies. Latent trajectory groups provided an opportunity to model different drug purchase patterns in time without fixed a priori assumptions about their number and nature. Consequently, different types of timing

of exposure during the three-year run-up period before the date of death/index date could be revealed.

However, our study also has some limitations, which should be taken into account when considering its results. Irrespective of the strengths of our register-based estimate of hypnotic drug use, it also has some uncertainties. It is somewhat uncertain how accurately register-based purchases reflect the actual usage of hypnotics. We did not analyse the amount or doses actually used, only the frequency of registered purchases. It is important, however, to note that actually used doses of hypnotics are impossible to estimate reliably based on purchase data. Hypnotics are drugs used “when needed”, which make them significantly different from, for instance, antibiotics or antihypertensive drugs, which are prescribed with specific daily doses to be used.

5.4 Conclusion

Although our data does not prove inferences on directions of causality behind the association of hypnotic use and increased mortality, it describes how the association is shaped by different drug use patterns in time in a more detailed way than previous studies. Taken together, these results give further evidence suggesting that in most cases, except perhaps some accidental injuries, the association is created without specific biological mechanisms by symptomatic treatment of discomfort caused by terminal illnesses. This conclusion is reassuring for patients and doctors in everyday clinical practice. It does not, however, mean that generally accepted guidelines to limit the use of hypnotics to the short-term use only and to increase nonpharmacological treatment in line should not be continued.

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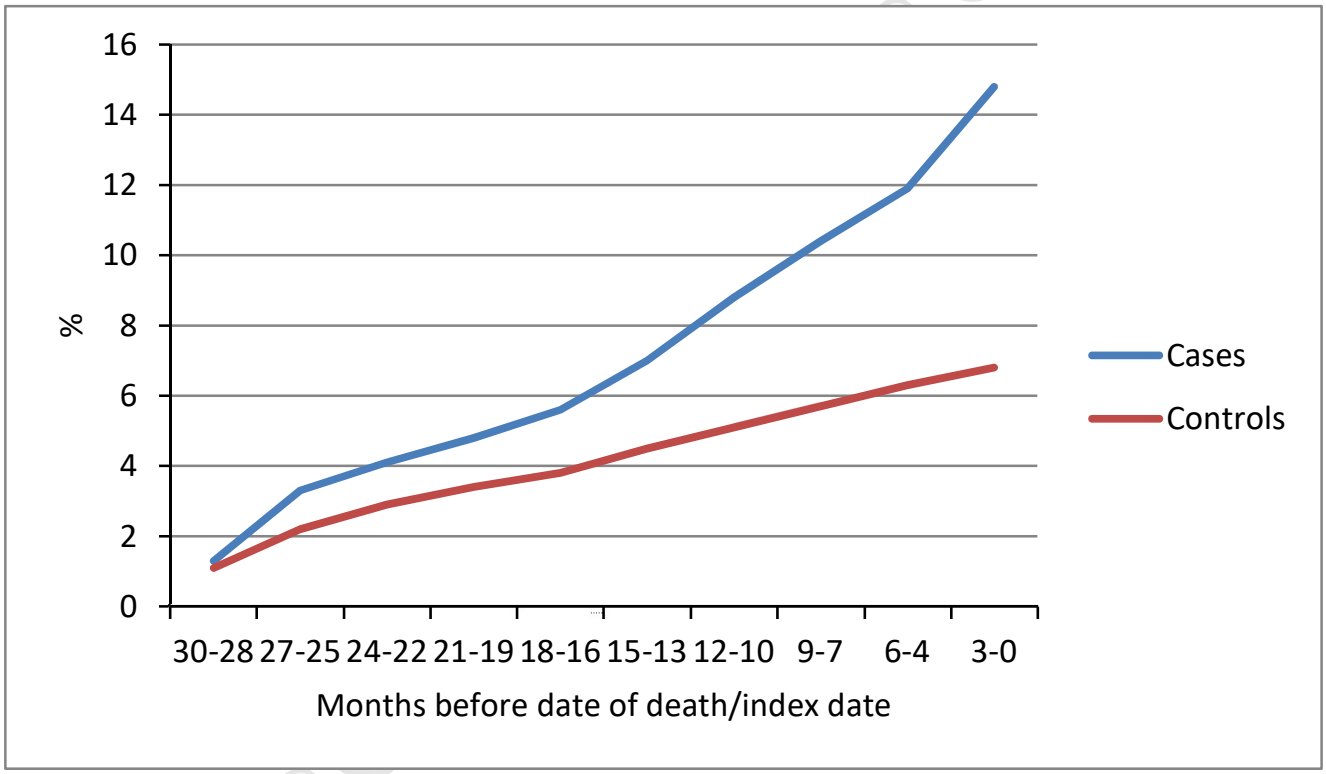

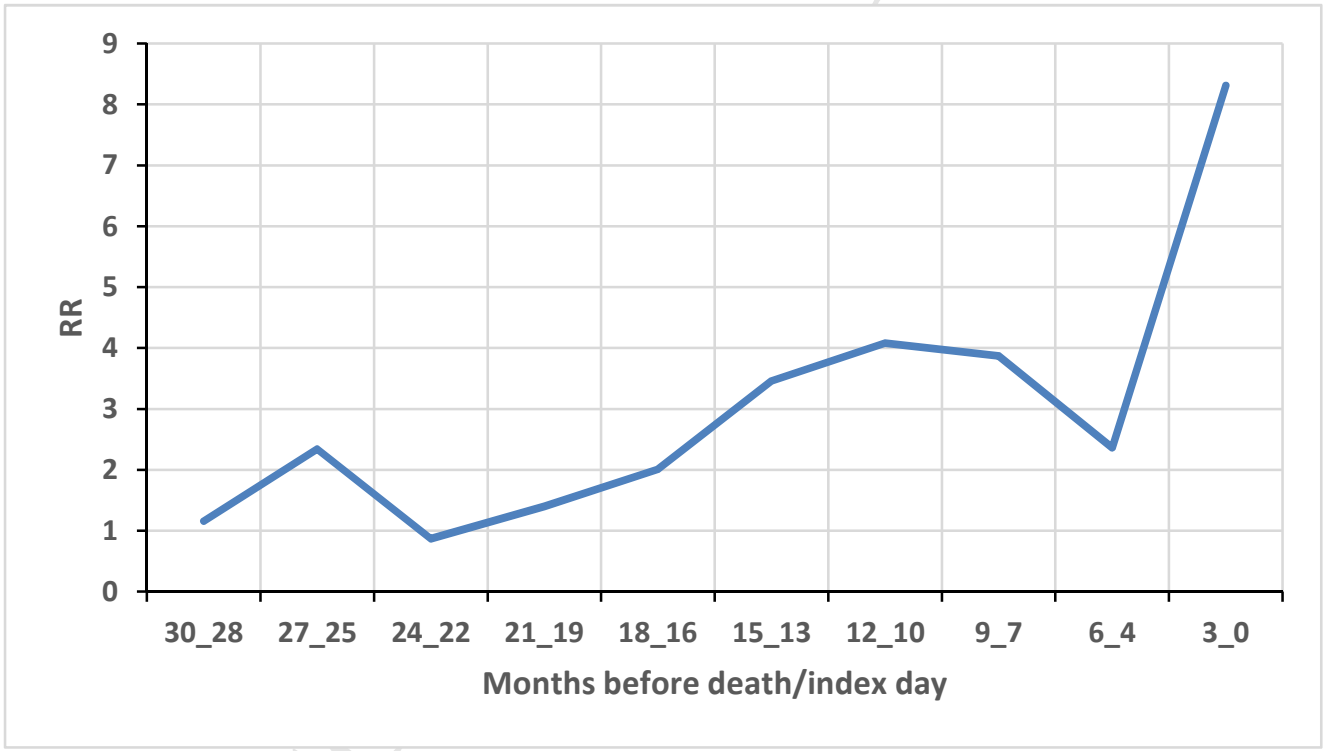

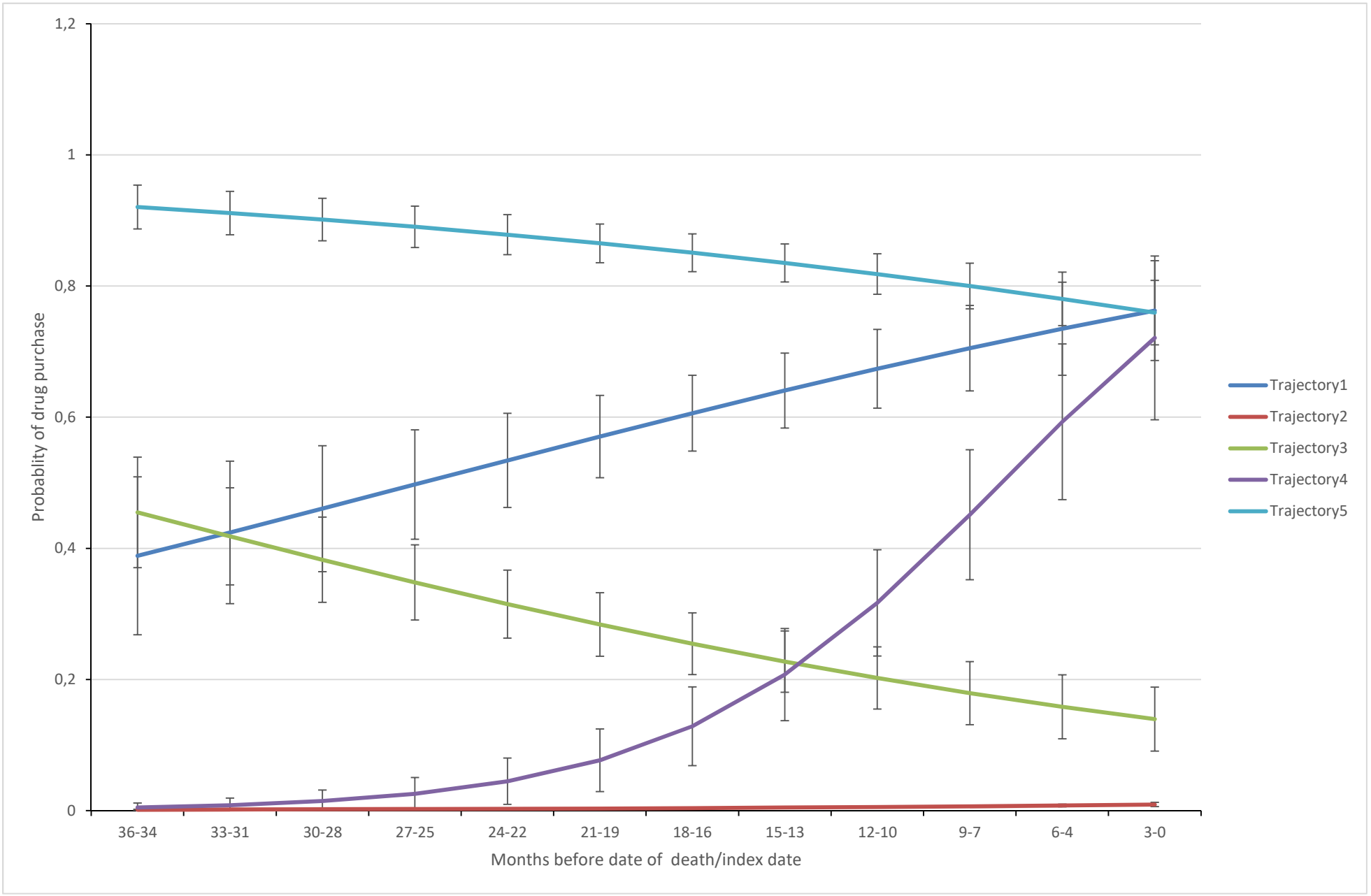
1,2
1
0,8
0,6
0,4
0,2
0
Probablity of drug purchase
36-34
33-31
30-28
27-25
24-22
21-19
18-16
15-13
12-10
9-7
6-4
3-0
Months before date of death/index date
Trajectory1
Trajectory2
Trajectory3
Trajectory4
Trajectory5

Association of hypnotic drugs with mortality is shaped by different drug use patterns

Different hypnotic drug use trajectories reflect different specific causes of death

Underlying mechanism is probably symptomatic treatment of terminal illnesses